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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,322	11/06/2001	Derry Roopenian	JL-2010	5668

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/07/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,322	ROOPENIAN, DERRY	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *1-29,31-46 and 65-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30 and 47-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group VIII, claims 30, 47-64, and species election for a candidate agent derived from an immunoglobulin Fc region, and an adult animal for drug delivery, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that groups I, III, IV, V, and VIII are closely related in nature as they encompass overlapping subject matter, namely transgenic mice with homozygous disruption in the endogenous FcRn gene, that these groups all belong to class 800, that a search of these claims would be co-extensive. This is not found persuasive because it is maintained that each of the Inventions requires a separate search status and consideration. Each of the groups I, III, IV and V is drawn to a different type of knockout/transgenic mouse and a different method of using such. For example, the transgenic mouse of group I only requires a disruption of endogenous FcRn gene, whereas the transgenic mouse of group IV requires the disruption of additional IgG gene, the transgenic mice of groups III and V require the presence of a human FcRn or/and IgG gene in the genome of the mice, which is not required for mice of groups II and I. The different transgenic mice are distinct in genomic structures, and thus, each would present a distinct phenotype. The search for these groups would have certain overlap, but they are not co-extensive. The inventions are further drawn to different methods of using the mice. For example, the methods of group IV and VIII are each drawn to using a mouse FcRn-/- and human FcRn+ transgenic mouse, however, the

method of group IV evaluate the effect of a pharmaceutical on the development of a disease, whereas the method of group VIII evaluate the half-life of IgG, for example, accordingly different methods have different method steps, and monitoring for different measurements, thus, require distinct search criteria and technical considerations.

Applicants further argue that MPEP § 803 requires that two criteria must be met for proper restriction. In response, M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02". (Emphasis added) Therefore, the criteria for restriction set forth in MPEP is met for the instant case, and it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Please also note, in light of the search results, all species in the elected group will be examined together in this Office action. Claims 1-80 are pending, however, claims 1-29, 31-46, 65-80 are withdrawn from further consideration by the Examiner,

pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 30, and 47-64 are under current examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not identify the provisional applications that this application claims priority to, which applications have been indicated in the application data sheet.

Specification

The abstract is objected to because the word "said" appeared twice in the abstract (lines 6 and 13). Applicant is reminded of the proper language and format for an abstract of the disclosure. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. Appropriate correction is required.

Claim Rejections

Claim 30 is objected to because "huFcRn" should be spelled out the first time it appears in the claim.

Claim 30 is objected to because an article should precede the word, "candidate inhibitor" in line 6.

Claim 47 is objected to because an article "the" should be inserted before "muFcRn-/-" in line 9.

Claim 52 is objected to because the word "a" before "either" in line 7 should be deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, and 47-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative

to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The methods recited in claims 30 and 47-64 require the use of two types of transgenic mice, the mFcRn -/-, and the mFcRn -/-, huFcRn+. The specification teaches the process of making the mFcRn-/- (Specification, pages 41-42) and the transgenic mouse expressing human FcRn gene (Specification, page 45), a clone 573 of FcRn-/-, and 5 clones of huFcRn Tg mice were established. The specification further teaches the process of producing muFcRn-/-, huFcRn transgenic mice by crossing the FcRn-/- and huFcRn Tg mice, and a clone of such mice was made. However, the specification fails to teach the ease or difficulty in making the mice required by the claims and since the mice are not commercially available, they cannot be routinely and reproducibly made in light of the state of the art of transgenic technology.

The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), this is particularly true in the art of transgenic animals with respect to transgene behavior and the consequence of gene knockout. Although the technique of making transgenic and knock out mice has become routine in the relevant art, the resulting genotype and phenotype varies significantly depending on the genes being manipulated, and the animals being used. Numerous art of record teach the phenotype unpredictability in transgenic animals. *Linder* (Lab Animal 2001 May;30:34-9) teaches "THE GENETIC BACKGROUND AND THE SURROUNDING ENVIRONMENT ARE OFTEN OVERLOOKED PARAMETERS THAT CAN SIGNIFICANTLY AFFECT THE OBSERVED PHENOTYPE", "OTHER FACTORS

INCLUDE MUTATIONS THAT ARE ACTUALLY HYPOMORPHS (I.E. MUTATIONS THAT CAUSE ONLY A PARTIAL DECREASE IN GENE EXPRESSION) RATHER THAN NULL ALLELES; COMPENSATORY PATHWAYS; AND TRANSGENESIS-SPECIFIC FACTORS, INCLUDING SITE OF INTEGRATION, TRANSGENE COPY NUMBER, AND INSERTIONAL MUTATIONS", "GENETIC BACKGROUND IS DEFINED AS A COLLECTION OF ALL GENES PRESENT IN AN ORGANISM THAT INFLUENCE A TRAIT OR TRAITS. WHILE MOST OF THE COMMONLY USED INBRED STRAINS SHARE A FAIRLY COMMON ORIGIN, EACH STRAIN HAS ITS OWN UNIQUE SET OF CHARACTERISTICS OR BACKGROUND LESIONS", "THE PHENOTYPE OF MICE CARRYING A MODIFIED GENE WILL VARY DEPENDING ON THE GENETIC BACKGROUND BECAUSE OF THE PRESENCE OF GENETIC MODIFIERS (ALLELIC VARIANTS AT LOCI OTHER THAN THE ONE BEING GENETICALLY MODIFIED) IN THE INBRED STRAIN GENOME" (see entire article). Without evidence to the contrary, transgene expression in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is supported by *Nebert et al. Nebert et al* (Biochemical Pharmacol 1997 Feb;53:249-54) teach the "neighborhood effect" in genome modification between different mouse strains, "IT HAS BECOME INCREASINGLY APPRECIATED THAT (A) JUST WHERE A TRANSGENE IS INSERTED, (B) HOW MUCH OF THE GENE SEGMENT IS REMOVED, AND (C) HETEROGENEITY OF THE GENETIC BACKGROUND OF THE KNOCKOUT LINE CAN ALL CONTRIBUTE TO DRAMATICALLY DIFFERENT PHENOTYPES. IT SHOULD BE APPRECIATED THAT, FOR EXAMPLE, A C57BL/6J (FROM JACKSON LABORATORY) AND A C57BL/6N (FROM NIH) HAVE DIVERGED FROM ONE ANOTHER FOR MORE THAN 45 YEARS AND, THEREFORE, SHOULD NOT BE CONSIDERED GENETICALLY IDENTICAL. The observation is further supported by *Mullins et al. Mullins et al.*(J Clin Invest 1996 Apr;97:1557-60) state, "THE MAJOR PROBLEM REGARDING PRONUCLEAR MICROINJECTION IS THAT THE EXOGENOUS DNA INTEGRATES RANDOMLY INTO CHROMOSOMAL DNA. POSITION EFFECTS, WHERE THE TRANSGENE IS INFLUENCED BY ITS SIT OF INTEGRATION IN THE HOST CHROMOSOME, CAN

HAVE MAJOR CONSEQUENCES ON THE EXPRESSION OF THE TRANSGENE, INCLUDING LOSS OF CELL SPECIFICITY, INAPPROPRIATE HIGH COPY NUMBER-INDEPENDENT EXPRESSION AND COMPLETE SILENCING OF THE TRANSGENE" (paragraph bridging pages 1557-58), "A GIVEN CONSTRUCT MAY REACT VERY DIFFERENTLY FROM ONE SPECIES TO ANOTHER" (page 1559, Summary). *Logan and Sharma* (Clin Exp Pharmacol Physiol 1999 Dec;26:1020-25) teach "PROBLEMS WITH OBTAINING EXPRESSION OF TRANSGENES IN ANIMALS HAVE BEEN RELATED TO THE INABILITY TO ROUTINELY OBTAIN HIGH LEVELS OF EXPRESSION, ESPECIALLY OVER MULTIPLE GENERATIONS, AND THE OBSERVATION OF VARIEGATED EXPRESSION, WHEREBY NOT ALL CELLS IN AN ORGAN WILL EXPRESS THE GENE. Thus, the making of the FcRn knockouts and phenotype resulting from random insertion of human FcRn in the mouse genome would expect to be varied and unpredictable.

For reasons set forth above, it is highly unpredictable whether the mice having the given phenotype required by the claims could be reproducibly made without undue experimentation. Accordingly, in view of the quantity of experimentation necessary to obtain the mice required by the claims, and the lack of predictability of the art, one skill in the art could not practice the invention without undue experimentation.

It is apparent that the FcRn-/- mice and the FcRn-/-, huFcRn+ mice are required for practice the invention. As such they must be readily available or obtainable by a repeatable method set forth in the specification or other wise known and readily available to the public. If it is not so obtainable or available, an enabling deposit of the mice may satisfy the requirements of 35 U.S.C. 112, first paragraph.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her

signature and registration number, stating the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Claims 47-64 require the use of "a trackable composition" attached to a candidate agent for FcRn-mediated drug delivery. The specification teaches, "The identity of the trackable composition may produce a physiological effect on mouse function or may simply be an easily detectable molecules e.g., through enzymatic

activity or recognition of or as an antigen" (Specification, page 23, lines 30-35). Given the broadest reasonable interpretation, the term embraces any substance that would produce a physiological effect on a mouse, any enzyme, and any antigen. However, the specification fails to teach, either by providing a list of substances or reduction to practice, a single example of the trackable composition that meets claim limitation, how it is attached to the candidate agent, and how the agents are being tracked; and it fails to teach how to quantitatively measure the physiological effect of the trackable composition and correlate the physiological effect with the characterization of the candidate agent, thus, fails to provide an enabling disclosure for the broadly claimed trackable composition. One skilled in the art would not know how to use the invention without first carrying out undue experimentation to determine how to track the composition as broadly claimed.

Claim 52 is drawn to identifying a candidate agent for FcRn-mediated drug delivery in the fetus comprising administering a formulation comprising a candidate agent to the pregnant FcRn-/-, huFcRn+ mice, and assaying for the blood of the fetus. However, the specification fails to teach how and whether it is feasible to obtain blood from the fetus of a mouse, and thus fails to provide an enabling disclosure to support the full scope of the claims.

The Federal Circuit court has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement.

> However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Since the specification fails to provide sufficient guidance for the specifics of the starting material, trackable agent, and the process of carrying out the assays for the trackable composition, it fails to provide sufficient guidance for the skilled in the art intending to practice the invention. Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49, 54, 57, and 60-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49 and 54 are vague and indefinite. The phrase "such as" used in these claims renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). A broad range or limitation together with a narrow range or limitation that falls within the broad range or

limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 49 and 54 recite the broad recitation "an FcRn binding partner", and the claims also recite "such as immunoglobulins or portions thereof", which is the narrower statement of the range/limitation.

Claim 60 recites the limitation "the engineered molecule" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 61 recites the limitation "the agent, formulated without the candidate agent" in line 12. There is insufficient antecedent basis for this limitation in the claim.

Claim 61 recites, "a trackable formulation comprising an agent linked to a candidate agent", here, it is unclear the function of "an agent" in the formulation, and how the formulation is "trackable", and thus, the metes and bounds of the claims are unclear.

Claim 61 is vague and indefinite because of the numerous inconsistent recitations of "an agent", "drug stability candidate" (lines 2-3), "a candidate agent" (line 5), and "the agent" (lines 12 & 17), for example. It is unclear the interrelations of the agent and candidate, and it is ambiguous with regard to which agent the recitations refer to. For example claim recitation, "the agent" in line 17 could refer to the agent formulated without the candidate agent or the agent linked to a candidate agent.

Claim 61 is vague and indefinite because it is unclear how determining the difference in half-life of the agent (step d) correlates with determining the pharmcokinetics of the agent (preamble), and what kind of difference indicates the pharmacokinetics of an agent. Specifically, the preamble of the claims calls for determining the pharmacokinetics of an agent, whereas the resolve of the methods recites, "determine the difference in half-life conferred to the agent by the candidate agent for FcRn mediated drug stability". Thus, it appears that the resolve of the method determines whether said candidate agent could confer the stability to the agent to which it linked to, rather than the pharmacokinetics of an agent. In fact, the pharmacokinetics of the agent is determined in step c, when the half-life of the formulation is determined.

Claim 64 recites the limitation "the engineered molecule" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

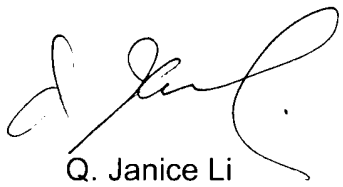
No claim is allowed. Claims 30 and 47-64 appear to be free of cited prior art of record, however, they are subject to other rejections/objections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).



Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
May 5, 2003